

The contrast agents of the present invention also may be used for certain therapeutic applications. More particularly, gadolinium oxide-containing microspheres can be used with neutron capture therapy in the treatment of cancer. Any procedure for neutron capture therapy known to those of skill in the art may be modified in accordance with the present invention. Generally, the composition of gadolinium oxide-containing microspheres can be prepared as described above. The gadolinium composition is administered intravenously and/or otherwise localized to a tumor. When the gadolinium nucleus is irradiated with neutrons, the gadolinium produces several forms of radiation, including γ -rays, x-rays, internal conversion electrons and Auger electrons, which help to kill the tumor. Because Gd_2O_3 has a very large thermal neutron capture cross-section (66 times larger than that of boron-10), the range of radiation and the corresponding killing efficacy are increased when compositions in accordance with the present invention are used.

In accordance with the present invention there is also provided a mathematical model that is free from certain limitations of the models currently being used for contrast agents. Additionally, the model is implemented into a simulation tool to characterize newly created multimodal agents and thereby to evolve improved designs with optimal characteristics.

A two-component simulation model is provided. The first part uses Boundary Element Method ("BEM") to solve for the potential flow. The second part uses a Finite Difference Time Domain ("3D-FDTD") model. This model uses the results of the BEM model to simulate the bulk behavior of encapsulated microbubbles in solution insonified by pulsed ultrasound waves. The 3D-FDTD method is used for the simulation of acoustic wave propagation and scattering in inhomogeneous media. This method exploits the true three-

dimensional aspect of the propagation problem by iteratively solving in time steps the equation of motion and the equation of continuity of the acoustic wave in the form of difference equations, hence the name Finite Difference Time Domain ("FDTD"). The advantage of the FDTD method is the ability to simulate complex structures in the time domain. This is especially important when dealing with biological structures. In addition, transient behavior as well as steady state behavior also can be studied with this method.

Although not always explicitly stated, the near field has always been modeled with incompressible potential flow assumption (radial velocity approximately $1/r^2$ at a distance r from the bubble center). The multi-scale rigorous mathematical model of the present invention considers an inner potential region near the bubble and an outer acoustic region far away. Rather than using a radial equation, a boundary element method is applied to solve for the potential flow in the near field, which furnishes nonlinear shape oscillation and, therefore, the directional information of the pressure and the velocity field around an agent. The velocity potential $\Phi(x)$ is obtained by solving the discretized integral equation:

$$\phi(x) = \int_S \phi(x_0) \frac{\partial G}{\partial n}(x - x_0) dS(x_0) - \int_S G(x - x_0) \frac{\partial \phi}{\partial n}(x_0) dS(x_0) \quad 15$$

where (x, x_0) is the Green's function of the Laplace equation $-\nabla^2 \phi = \delta(x - x_0)$. The pressure and the velocity fields obtained at the inscribing surface, $\partial\Omega_s$, are used to compute the scattered far field in the acoustic region. In the far field the flow is compressible yet linear:

$$(\nabla^2 + k_m^2)\phi(x) = 0 \quad 20$$

where k_m is the wave number based on the effective sound speed in the medium containing agents. This equation is solved for the velocity, $\partial\Phi/\partial n$, given the values of Φ at the surface.

On the other hand, Φ at the surface is obtained by the Bernoulli's equation, valid in a potential flow:

$$\frac{\partial \phi}{\partial t}(\mathbf{x}) + \frac{1}{2} |\nabla \phi(\mathbf{x})|^2 = \frac{p_{\infty} - p_L}{\rho}$$

The effects of internal pressure due to vapor (v) and gas (g) and surface tension (σ) are
5 represented in the liquid pressure p_L at the outer wall of the agent:

$$p_L = p_v + p_g - C\sigma$$

C being the curvature of the bubble surface.

Most contrast agents are made with an encapsulating shell, however, very little is known about shell properties, which vary in thickness, number of layers and other
10 characteristics, depending on the method used to create them. As mentioned before, various models have been proposed with various degrees of detail for the elastic shell. In Church's solution it is assumed that a continuous layer of incompressible, solid elastic material separates the gas from the bulk Newtonian liquid. A Rayleigh-Plesset-like equation describing the dynamics of such surface-contaminated gas bubbles was derived. Church
15 found that the resonance frequencies of individual bubbles tend to increase as the modulus of rigidity increases. Encapsulated bubbles with shell rigidity greater than approximately 85 mega pascals (MPa) provide a greater cross section per unit attenuation in the lower biomedical frequency range than do free bubbles of the equivalent size.

The need to simultaneously incorporate both non-linearity and directionality is
20 addressed by the present model. Non-linearity is essential for harmonic and transient power scattering, both of which promise better discrimination against background tissue signals. On